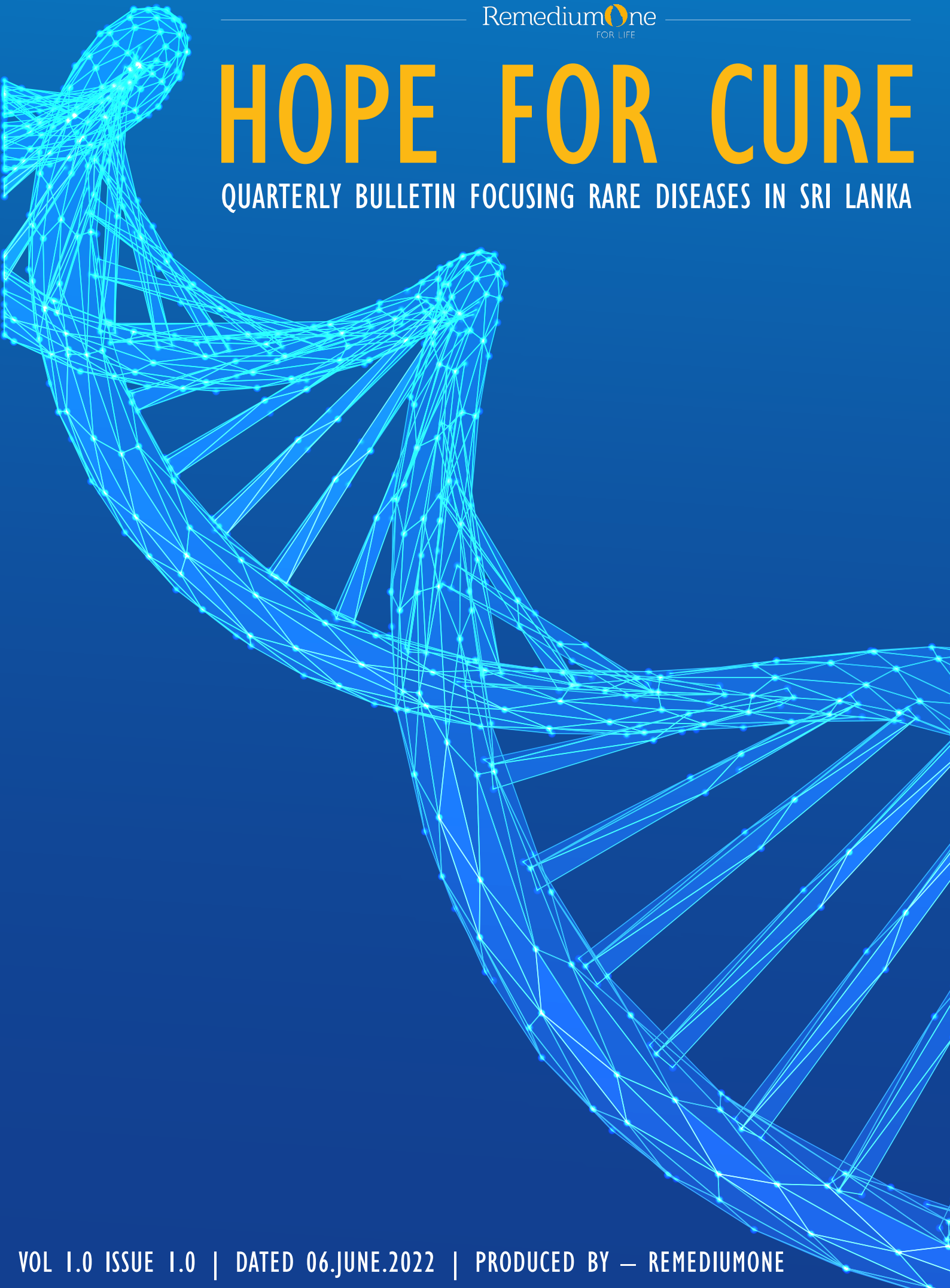
RemediumOne
FOR LIFE

HOPE FOR CURE

QUARTERLY BULLETIN FOCUSING RARE DISEASES IN SRI LANKA



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HOPE FOR CURE

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Why "Hope for Cure"

Today, Sri Lanka is recognised globally for its success in mitigating diseases, promoting the health of its people, and implementing global health initiatives. The improvements in health indicators, extending advantages of good healthcare to poor and marginalised populations. Sri Lanka's achievements in the sphere of the control of communicable diseases are commendable. However, the country experiences outbreaks of infectious diseases such as dengue.

Rare diseases are an important public-health issue and a challenge for the medical community in Sri Lanka. Lack of patient registries, advanced genetic testing facilities and awareness among patients are some of the major challenges. Sri Lanka being a middle-income country having 23 million population directing patients towards potential cure for rare disses is challenging. Many endeavors are currently taken by key organisations in Sri Lanka to mitigate this problem.

As a responsible clinical research organisation RemediumOne has envisioned to bring "Hope for Cure" quarterly bulletin to highlight key challenges Sri Lankan patients are facing now to find cure to rare disease conditions. We are hoping to focus on Key Medical Practitioners in Sri Lanka who are interested in finding cure for rare diseases and patients. We believe that this bulletin will be a platform to share information concentrated on Sri Lanka and rare diseases with international research community.

As an organisation we will be delighted if we could bring cure to Sri Lankan patients who are suffering with orphan diseases.

Thalassaemia, a significant public health problem in Sri Lanka

Key Points:

- Thalassaemia, a rare disease in Sri Lanka, has been a significant public health issue for many decades.

- Sri Lanka at present records around 2000 thalassaemia disease affected patients.

- A recent cross-sectional nationwide survey of hospital-based thalassaemia patients, collected data on 1774 patients from 23 centres.

- Thalassaemia is a condition which requires lifelong treatment.

Rare Diseases are defined as conditions that affect fewer than 1 in 2000 of the population, excluding infections. The accurate diagnosis of most of these diseases requires sophisticated laboratory investigations, therefore, poses a great challenge to paediatricians in low- and middle-income countries. To overcome these limitations, the rare disease forum of the SLCP attempts to develop international collaborations with high-income countries, obtain government funding for expensive investigations and to liaise with drug regulatory authorities to make medicines available for children with rare diseases. The rare disease forum also maintains a database of all rare diseases reported in Sri Lanka, which will facilitate the diagnosis, reporting and management of Rare Diseases in Sri Lanka.

Thalassaemia, which is a rare disease in Sri Lanka, has been a significant public health issue for many decades. As managing the increasing number of patients found to be a burden to the health system, the emphasis was given to the prevention of new thalassaemia births. Sri Lanka at present records around 2000 thalassaemia disease affected patients, and the majority of them have beta-thalassaemia major and HbE beta-thalassaemia.

My current involvement in thalassaemia disease management is in the capacity of the Paediatrician-in-charge of the Paediatric thalassaemia unit of Colombo North Teaching Hospital, Ragama, Sri Lanka. Colombo North Teaching Hospital is a tertiary care referral centre and is a national referral centre for the diagnosis and management of thalassaemia, and as a clinician, I lead the multidisciplinary team caring for patients with thalassaemia. Furthermore, at present, I lead clinical research on thalassaemia and iron deficiency anaemia which are the two most common paediatric haematological conditions in the country.

A recent cross-sectional nationwide survey of hospital-based thalassaemia patients, for which I was an Investigator, collected data on 1774 patients from 23 centres. The study reported that 1219 patients (68.7%) had homozygous β-thalassaemia, 360 patients (20.3%) had haemoglobin E β-thalassaemia, and 50 patients (2%) had sickle β-thalassaemia. Also, there were unacceptably high serum ferritin levels in patients from almost all centres, and the annual number of births of patients with β-thalassaemia varied between 45–55, with little evidence of reduction over 19 years.

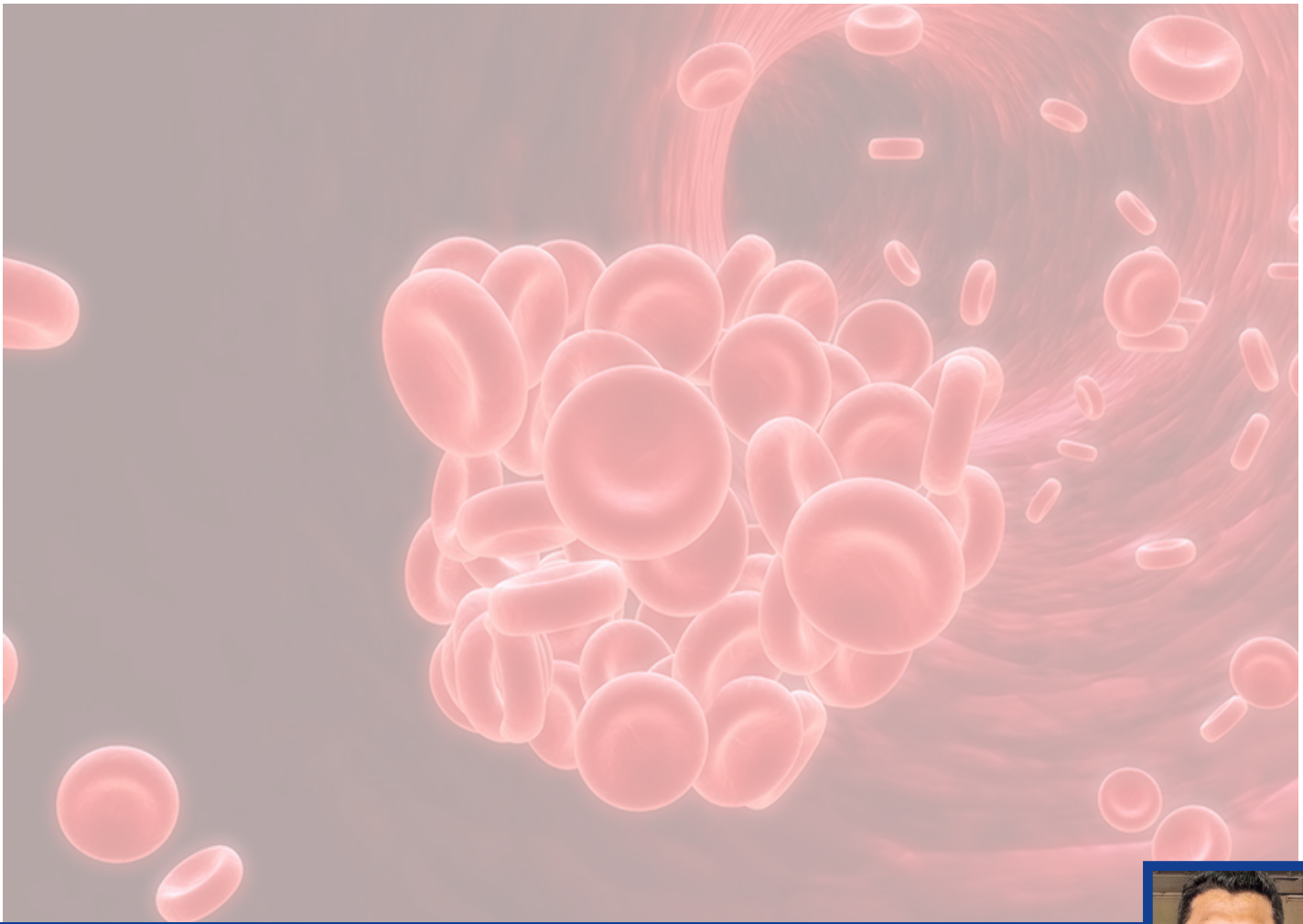
Within the first two years of life, the majority of children with moderate to severe thalassaemia show signs and symptoms, and this can be diagnosed with HPLC (High Performance Liquid Chromatography).

Prof. Sachith Mettananda
Consultant Paediatrician and Head of Department of Paediatrics,
Faculty of Medicine, University of Kelaniaya

Despite the fact that prenatal diagnosis by amniocentesis has been practised worldwide for many years, genetic diagnostic facilities were not available in Sri Lanka until recently.

Thalassaemia is a condition which requires lifelong treatment. Treatment calls for the necessity for the patient to receive blood transfusions on a monthly basis. This is the main and most common treatment received by thalassaemia patients in Sri Lanka. However, at present, there appears to be a cure through bone marrow transplantation though this is a possibility only open to a minority of the patients in Sri Lanka.

It is essential for novel developments in treatment for thalassaemia to go in parallel with programs that guarantee access to patients in resource-limited countries since the majority of thalassaemia patients live in such regions. Sri Lanka possesses locally and overseas educated and experienced healthcare professionals and thereby ensuring a high standard of disease management regimes. The well-developed healthcare system in Sri Lanka has the necessary infrastructure and expertise to carry out advanced research and clinical trials pertaining to rare diseases such as thalassaemia.



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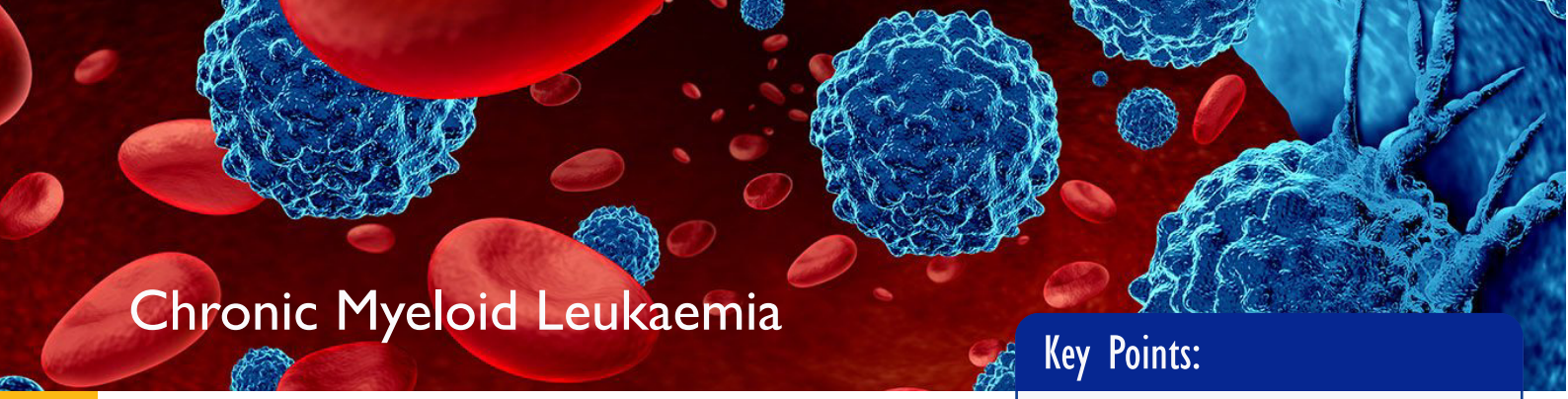


Chronic Myeloid Leukaemia

Key Points:

- CML is a significant global health burden and in Sri Lanka recent statistical data shows a gradual increase in the cases.

- The diagnosis of CML often occurs during a routine physical examination or blood test.

- Availability of highly competent and skilled medical professionals in Sri Lanka including haematologists and oncologists assures quality of the treatment regimes.

- The Sri Lanka College of Hematologists is one of the leading organizations conducting studies on CML.

My role as a Consultant Haematologist at the Department of Pathology, Faculty of Medicine, University of Kelaniya attracted me to involve myself in research and therapeutic studies on Chronic Myeloid Leukemia and Biodosimetry. It is because only limited trial research have been conducted on these diseases in Sri Lanka. Some of the topics that I have published over the recent years in peer reviewed journals are splenic syndrome in a young man at high altitude with undetected sickle cell trait, spontaneous micronuclei formation in persons living in Sri Lanka in close proximity to a nuclear power plant in India, higher rejection rates of paternal vs. maternal fully matched bone marrow grafts after ATG-Busulfan-Cyclophosphamide conditioning in children with thalassemia, bone marrow transplantation.

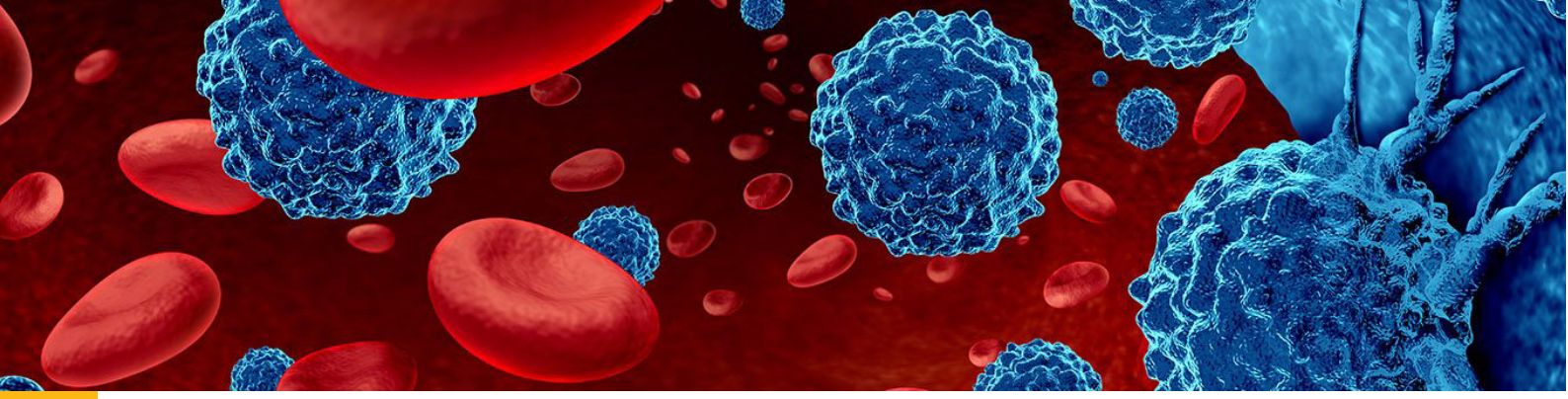
Chronic myeloid leukemia (CML) is a chronic myeloproliferative neoplasm. Although it is usually associated with the elderly, accounting for 20% of adult leukemias, it can almost affect anyone at any age. CML affects over 100,000 patients worldwide every year and represents a significant global health burden. In Sri Lanka recent statistical data shows a gradual increase in the cases reported, which may be due to better reporting rather than a true incidence. Nevertheless, information on CML incidence and prevalence is scarce.

The diagnosis of CML often occurs during a routine physical examination or blood test. Determining the phase of the disease i.e., chronic phase, accelerated phase or blast crisis is important at diagnosis. Sri Lanka, boasts of a state funded health care system, assuring its' facilities accessible to all its' citizens free of charge. Investigational procedures and screening laboratory tests are available in both the government hospitals as well as private facilities. Most patients with CML are treated at the National Cancer Institute Maharagama, as well as tertiary care centers in Sri Lanka by consultant haematologists, haemto-oncologists, as well as oncologists.

The current treatment regimes used in Sri Lanka to treat CML are Imatinib, Nilotinib, and Dasatinib, as first line therapy from which Imatinib is the most widely used. The other specific treatment options in practice are allogeneic stem cell transplantation, hydroxycarbamide and Interferon alpha. CML is being studied in clinical trials around the world, for newer tyrosine kinase inhibitors which may achieve faster, deeper and more sustainable molecular remissions, as well as attain treatment free with durable remissions.

Availability of highly competent and skilled medical professionals in Sri Lanka including haematologists and oncologists assures quality of the treatment regimes. The Sri Lanka College of Haematologists is one of the leading organizations conducting studies on CML.

Prof. Senani Williams
Consultant Haematologist and Senior Professor at ,
Faculty of Medicine, University of Kelaniaya



Sri Lanka College of Haematologists has published several articles in the Journal of Haematology and has also issued guidelines pertaining to various haematological diseases inturn improve standard of clinical management and leading to standardized care to the patient which help improve standards of health leading to betterment of the society. The Sri Lanka College of Haematologists is in collaboration with the American Society of Haematology and the European Haematology Association in facilitating the educational programmes among haematologists and their peers to seek consultation on clinical cases related to myeloproliferative disorders, anemia, etc. The infrastructure and healthcare system prevailing in the country makes Sri Lanka a preferred destination to conduct advanced research and clinical trials on CML.

RemediumOne initiative of publishing on rare disease bulletin is highly commendable and definitely a positive step towards broadening the horizons of clinical research in CML in this region.

Prof. Senani Williams
Consultant Haematologist and Senior Professor at ,
Faculty of Medicine, University of Kelaniaya

Acromegaly - A Rare Endocrine Disorder

Key Points:

- Acromegarly; A rare disorder characterized by an excess secretion of growth hormone (GH)

- Nearly 100 patients with acromegaly have been encountered over the last 8-10 years at the National Hospital of Sri Lanka.

- Availability and cost can limit the use of medical therapy in our part of the world.

- Sri Lanka as a trial destination with international standard health system and availability of required infrastructure and expertise.

Endocrine disorders are often complex and rare, require a long period of careful evaluation and follow up. Due to the intrinsic features of hormone action and the genetic basis of some conditions, the consequences of endocrine disorders are usually not restricted to a single organ, but instead overlap in multiple organ system. Therefore, it is of vital importance that the unmet needs of patients with rare hormonal disorders are met by an overarching network with a broad expertise covering all endocrine glands and challenges from birth until adulthood.

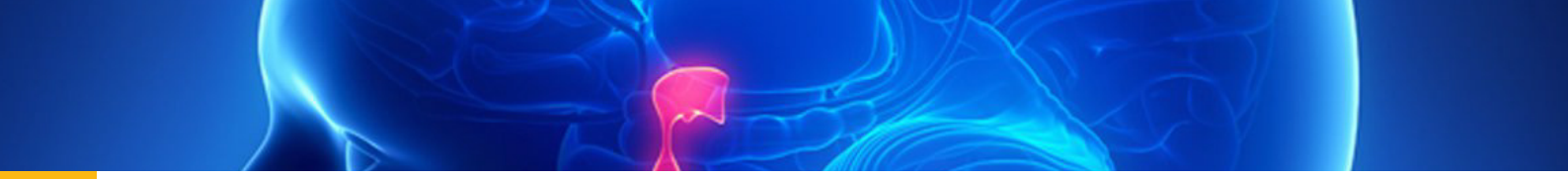
Acromegaly is a rare disease characterized by slow progressive acral (acro) enlargement (megaly) resulting from excess growth hormone (GH) subsequently leading to excess insulin like growth factor-1 (IGF-1), in most cases due to a GH secreting pituitary adenoma and in rare instances due to pituitary hyperplasia or ectopic GH or GH-releasing hormone (GHRH) secretion. The term 'Acromegaly' was coined by Pierre Marie in 1886, a French neurologist when he described the distinguishing features of this complex disease in a 37-year-old lady. If the excess GH secretion begins before the end of puberty and epiphyseal closure; hence with an accelerated linear growth, it is termed as 'Gigantism'.

The estimated prevalence is 40-70 patients per million of the general population, although recent estimates suggest an increase in incidence. Median age at diagnosis is 40-50years with a significant interval delay from the onset of symptoms to the time of diagnosis (roughly 12years) due to the insidious onset and very slow progression of the disease. Thus, at the time of presentation majority have macroadenomas (tumor diameter >10mm) and some with significant extrasellar extension.

As of now, there aren't any published data on the prevalence of this disorder in Sri Lanka. At the National Hospital Sri Lanka, a leading referral center and a tertiary care hospital, we have encountered nearly 100 patients with acromegaly over the last 8-10 years.

Symptoms and signs of acromegaly are brought by the effects of excess GH and IGF-1, mass effect from the tumor and pituitary hormonal imbalance. Overgrowth of soft tissue in the extremities leads to large hands and feet increasing the ring size and shoe size noted by the patients over time, macrognathia, macroglossia, coarsening of facial features can lead to marked social embarrassment. Hypertension, arrhythmia, cardiomyopathy, cardiac hypertrophy are common cardiac manifestations while approximately 3-10% of patients can present with heart failure.

Dr. Manilka Sumanatilleke
Consultant Endocrinologist, National Hospital of Sri Lanka



Diagnosis of Acromegaly

Diagnostic evaluation of a patient with typical features suggestive of acromegaly starts with measurement of IGF-1, which provides excellent discrimination from normal individuals. An unequivocally elevated IGF-1 level in an acromegalic patient confirms the diagnosis whereas a normal IGF-1 level is strong evidence against the diagnosis. However, the gold-standard dynamic testing for acromegaly is OGTT with serial GH measurement, where a nadir GH level of <1µg/L within two hours after an oral glucose load usually excludes the diagnosis. Once biochemically confirmed the next step in diagnosis is to image the patient with MRI.

Treatment for Acromegaly

The primary goals of therapy in acromegaly are to normalize the IGF-1 for patient's age and gender, reduction of GH level <1µg/L, control the tumor size and mass effect on the surrounding structures, improve the systemic manifestations. The initial therapeutic approach is personalized, although transsphenoidal surgery remains the primary treatment in majority. Pathology is useful to categorize the tumor further, including investigation of tumor aggressiveness (such as with Ki-67 index), presence of dural invasion, degree of granulation, or atypical appearance of the cells. Outcomes of surgical management with experienced pituitary surgeons, microscopic or endoscopic trans sphenoidal microsurgery results in an initial remission rate 85% for micro adenomas and 40 – 50% for macro adenomas. Cavernous sinus invasion indicates a tumor that is surgically unresectable. Five-year disease recurrence rates range from 2 to 8%.

Medical therapy is recommended for those who have persistent disease despite of tumor resection or in whom surgery is contra-indicated/ inappropriate. The available options are wide, though availability and cost can limit the use of them in our part of the world. Somatostatin receptor ligands (SRLs) or pegvisomant should be considered as a first line therapy in patients with significant disease (ie, with moderate-to-severe signs and symptoms of GH excess and without local mass effects). Radiation therapy should be considered in the setting of residual tumor mass following surgery, and if medical therapy is unavailable, unsuccessful, or not tolerated. Stereotactic radiotherapy is preferred over conventional radiation therapy in patients with acromegaly, unless the technique is not available, there is significant residual tumor burden, or the tumor is too close to the optic chiasm resulting in an exposure of more than 8 Gy. Radiotherapy may even be considered in the setting of an aggressive tumor, including the presence of high Ki-67 staining. An advantage of radiation therapy is that it may result in biochemical control, thereby limiting the need for a lifelong medical therapy. However, the full therapeutic effect of radiation therapy may take many years, and a subset of patients may have limited response. Therefore, medical therapy is required while awaiting the response to radiation therapy.

The rarity of the disease necessitates large population studies for the generation of reliable epidemiological data. Acromegaly treatment has been shaped by periodic publication of clinical guidelines and consensus statements, based on evidence-based recommendations and clinical expertise of the participants. Just as methodology of clinical trials has changed over time, there have also been changes in the trends of acromegaly clinical care. The clinical trials should be inclusive of a diverse population as to study differences in safety and effectiveness of interventions across subpopulations. Sri Lanka is well equipped to participate in clinical trials of international standard, due to our well-defined health system and availability of required infrastructure and expertise.

Dr. Manilka Sumanatilleke
Consultant Endocrinologist, National Hospital of Sri Lanka

Diagnosing Rare diseases

Key Points:

- A variety of genetic tests for diagnosis with free of charge from Sri Lankan government sector.

- Sri Lankan public and private health sector provides a massive collaboration with excellent diagnostic options for rare disease patients.

As per the year one report of the Global Commission to End the Diagnostic Odyssey for Children with a Rare Disease, it takes a minimum of five years to diagnose a child with a rare disease, even in countries with sophisticated health systems. The delay to diagnose is attributed to many factors including the lack of access to diagnostic tools, the lack of awareness about the disease, poor communication among healthcare providers, the lack of physician training with regard to rare diseases, and the lack of geneticists. The effects of these deficiencies are felt both globally and locally.

In Sri Lanka, inherited rare diseases can be diagnosed with a variety of genetic tests. These could range from simple tests that examine chromosomes (a karyotype) or the change of one nucleotide base in a gene (DNA) to tests that examine an entire gene or even all the genes (an exome).

In the public health sector of Sri Lanka, which provides its services free of charge, the Human Genetics Unit (HGU) at the Faculty of Medicine of the University of Colombo (UoC) has been at the forefront for using genetic testing as a means of detecting genetic defects to identify rare diseases. The HGU gets referrals of clinical diagnoses from around the country. But despite being internationally recognised for being extremely resourceful in a low-resourced setting, the lack of funding and the lack of awareness have hindered their ability to serve in their fullest capacity.

In the private health sector, Genelabs and Credance Genomics are some of the facilities that have the diagnostic tools to examine hundreds to thousands of critical changes or misspellings of the genetic code known as mutations in diagnosing a health status in question.

Why Hope for Cure – From RemediumOne Perspective

Key Points:

- Sri Lanka has the capacity to execute rare disease projects as per international standards.

- RemediumOne has associated with more than 25 principal investigators, who has prior trial exposures in the field of rare diseases.

- RemediumOne, a trusted partner to world's leading Centers of Excellence such as University of Oxford.

- Through "Hope for Cure" hope to raise awareness of the rare diseases prevalent in Sri Lanka and available treatments

Ever since passing out from Medical Faculty in 2006, I had a passion towards Clinical research, and I was recruited to the Clinical Trails Unit (CTU) Pharmacology Department University of Kelaniya as a Clinical Research Coordinator. After RemediumOne was founded in 2009, I continued my work in Clinical Operations for many years leading a team of 45+ staff in my department. In this role, the RemediumOne team was able to perform many global multi-center randomised Phase II and Phase III clinical trials that have been conducted at leading state hospitals in Sri Lanka for more than 10 Years. RemediumOne has created a high-quality platform for many sponsors and CROs to work in Sri Lanka.

We have managed successful completion of more than 10 clinical trials on rare diseases in the fields of Oncology, Nephrology, Endocrinology, Hematology, Paediatrics and Rheumatology, which have engaged 80+ participants. Through these trials RemediumOne has associated with more than 25 principal investigators, who has prior trial exposures in the field of rare diseases.

Sri Lanka has the capacity to execute rare disease projects as per international standards because we at RemediumOne provide complete management services from submission to close out, achieved by identifying highly qualified medical specialists and supporting their study teams with well-trained, determined, and diligent coordinators with an uncompromising focus on quality. RemediumOne has an excellent rapport with these highly qualified investigators and pride on being the only ISO 9001:2015 and ISO 27001 certified medical research organization in Sri Lanka.

RemediumOne is a trusted partner to world's leading Centers of Excellence such as University of Oxford, Duke University, The George Institute for Global Health, University of Nottingham, Duke-NUS Graduate Medical School, Public Health Research Institute, Canada, etc. and takes pride in continued collaborations with them.

Clinical trials can be a crucial opportunity to access life-saving treatments and having lack of representation results in drugs being developed that aren't proven safe or effective across different populations. Hence, this raises the importance of relying on data from multicenter, large clinical trials representative of the global patient population; and more importantly, the need for continued data generation through real-world evidence. This is our first issue in the series of Hope for Cure. Through this quarterly newspaper, we hope to raise awareness of the rare diseases prevalent in Sri Lanka.

Dr. Namal Wijesinghe
Head of Clinical Operations, RemediumOne

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